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APPLICATION NUMBER: ***60/529,534***
FILING DATE: ***December 15, 2003***
RELATED PCT APPLICATION NUMBER: ***PCT/US04/42474***

Certified By

Jon W Dudas

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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Todd Duncan	Campbell	Petaluma, California

Additional inventors are being named on the One *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Alginate Coating with Therapeutic and Cellular Components

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ Customer Number:

OR

☒ Firm or Individual Name	James F. Hensel				
Address	2911 SW Orchard Hill Place				
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City	Lake Oswego	State	OR	Zip	97035-1194
Country	USA	Telephone	503-244-3232	Fax	

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* Cover and 25 Pages
☒ Drawing(s) *Number of Sheets* Five
☐ Application Date Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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[Page 1 of 2]

Respectfully submitted,

SIGNATURE [signature]

TYPED or PRINTED NAME James F. Hensel

TELEPHONE 503-244-3232

Date December 15, 2003

REGISTRATION NO.
(if appropriate)
Docket Number:

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This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Docket Number

INVENTOR(S)/APPLICANT(S)

Given Name (first and middle [if any]	Family or Surname	Residence (City and either State or Foreign Country)
James Finley	Hensel	Lake Oswego, Oregon

Number 1 of 1

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 80

Complete if Known	
Application Number	
Filing Date	
First Named Inventor	Todd Duncan Campbell
Examiner Name	
Art Unit	
Attorney Docket No.	

METHOD OF PAYMENT *(check all that apply)*

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FEE CALCULATION

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1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	80

SUBTOTAL (1) ($) 80

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

		Extra Claims	Fee from below	Fee Paid
Total Claims	-20** =		X	=
Independent Claims	- 3** =		X	=
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) ____________

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SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	James F. Hensel	*Registration No. (Attorney/Agent)*		*Telephone*	503-244-3232
Signature				*Date*	12/15/03

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Endolumen Therapeutics, Inc.
2911 SW Orchard Hill Place
Lake Oswego, OR 97035

December 15, 2003

Commissioner for Patents — **Via** Express Mail
Mail Stop Provisional Patent Application
Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

RE: Provisional Patent Application

Dear Commissioner:

Please find enclosed the following:

Provisional Patent Application Titled: "ALGINATE COATING WITH THERAPEUTIC AND CELLULAR COMPONENTS" including:

a. Provisional Application Coversheet (two pages);
b. Fee Transmittal;
c. Specification consisting of a cover page and 25 additional pages;
d. Drawings consisting of five pages; and
e. Check payable to the Commissioner of Patents in the Amount of $80 (claiming small business entity status).

Warm regards,

James F. Hensel

U.S. PROVISIONAL PATENT APPLICATION

ALGINATE COATING WITH THERAPEUTIC AND CELLULAR COMPONENTS

INVENTORS

Name: Todd Duncan Campbell

Name: James Finley Hensel

CORRESPONDENCE:

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2911 SW Orchard Hill Place

Lake Oswego, OR 97035-1194

ALGINATE COATING WITH THERAPEUTIC AND CELLULAR COMPONENTS

FIELD OF THE INVENTION

The present invention relates generally to endolumen therapeutics, and more specifically to alginate stent coatings with therapeutic and cellular components.

BACKGROUND OF THE INVENTION

The human body has numerous vessels and organs that transport bodily fluids for nutrient delivery, recirculation and excretion of byproducts. Many of these structures have a tubular geometry, for example, blood vessels, the intestinal tract, and the bladder. Even relatively solid organs such as the heart, liver, kidney and pancreas have tubular cavities and lumens. Disease processes such as tumors and aneurysms may create spaces or voids within otherwise solid organs.

The lumens afforded by organs and vessels can be affected by a variety of diseases and medical conditions. For example, a lumen may be occluded, thus limiting or blocking flow through the lumen. Since the lumen of many organs and vessels serve vital functions such as providing a conduit for blood, urine, bile, or food, restriction of flow through the lumen is usually undesirable. The growth of an occluding atheroma in an artery is an exemplary restriction that impedes blood flow.

Devices, materials and methods for the treatment and repair of tissues around vessel or organ lumens continue to be developed to minimize or eliminate restrictions within the lumens. Many of the newer treatments access the medial, endomural zone of organs, organ components or vessel tissues via surgical or percutaneous procedures. With many of these treatment procedures, inflammation, proliferative regrowth, and excessive ingrowth of tissue may occur in response to the trauma or vascular damage near the treatment area, lessening clinical effectiveness.

Medical researchers of coronary disease, for example, are working to develop better medical practices for inhibiting stenosis, the narrowing or constricting of a blood vessel lumen, and for preventing or minimizing restenosis that may occur after a procedure such as angioplasty. Atherosclerosis, which is characterized by the progressive buildup of hard plaque in the coronary arteries, as well as other types of stenoses are treated by a number of procedures, including balloon dilatation, stenting, ablation, atherectomy or laser treatment.

Although angioplasty and stenting procedures are probably the best-known procedures, other treatments are available for stenosis within vessels. In cases of severe atherosclerotic obstructions, endovascular removal of obstructive lesions via endovascular atherectomy, a catheter-based cutting or drilling procedure from within the vessel, may be employed. For example, directional coronary atherectomy involves a small sharp blade directed from inside a catheter to cut and ablate plaque from the wall of the artery. For another example, rotational atherectomy or rotablation procedures drill through plaque with a diamond-coated burr and pulverize the buildup of cholesterol or other fatty substances into small particles that can enter the bloodstream. While these procedures remove the diseased atheroma close to the vessel lumen and treatment device, they do not address the source or core of the disease that often lies in the vessel media.

One common minimally invasive medical procedure for treating various coronary artery diseases is percutaneous transluminal coronary angioplasty (PTCA), also called balloon angioplasty. PTCA can relieve myocardial ischemia by reducing lumen obstruction and improving coronary flow. After a catheter is introduced into a blood vessel and advanced to a treatment site, a small dilating balloon at the distal end of the catheter is passed across an atherosclerotic plaque and inflated to compress the plaque and expand an occluded region of the blood vessel. This compression cracks or otherwise mechanically deforms the lesion and increases the lumen size of the vessel, which in turn increases blood flow. In PTCA, the blockage is not actually removed, but is compressed into the arterial walls.

A medical prosthesis such as an intravascular stent may be used to mechanically keep the vessel lumen open and prevent post-angioplasty vessel reclosure. One common

catheter procedure delivers the stent prosthesis in a compressed form to the treatment site where the stent expands via the inflation of a catheter balloon or through self-expansion to engage the lumen wall of the coronary or peripheral vessel. Commercially available stents are fabricated from metals, alloys, or polymers and remain in the blood vessel indefinitely. Stent manufacturers have developed stents of various diameters and lengths to allow anatomic flexibility, although the stents may not be flexible enough to conform completely to the shape of the vessel being treated. In some cases, a stent itself can cause undesirable local thrombosis, create restenosis due to over-expansion within the vessel, or result in metal ion migration from the stent latticework.

While PTCA represents therapeutic advances in the treatment of coronary artery disease, vessel renarrowing or reclosure of the vessel often occurs after PTCA, due in part to trauma of the vessel caused by the balloon dilation or stent placement. In some cases, the vessel reverts either abruptly or progressively to its occluded condition, limiting the effectiveness of the PTCA procedure.

Restenosis, the gradual narrowing of a vessel, can occur after interventional procedures such as stenting and angioplasty that traumatize the vessel wall. Such trauma may lead to the formation of local thrombosis or blood clotting, which is most likely to occur soon after an intravascular procedure. To address the problem of thrombosis, patients receiving stents may receive extensive systemic treatment with anti-coagulants such as aspirin and anti-platelet drugs.

An uncontrolled migration and proliferation of smooth muscle cells, combined with extracellular matrix production, may develop during the first three to six months after a procedure when vessel trauma occurred. Scar-like proliferation of endothelial cells that normally line blood vessels may incur restenosis, and with stent placement, there may an ingrowth of tissue proliferation or inflammatory material through the interstices of the stent that can block and occlude the vessel.

Unfortunately, restenosis frequently necessitates further interventions such as repeat angioplasty or coronary bypass surgery. Alternative procedures, such as delivering radiation with intracoronary brachytherapy, have been used in an effort to curtail overproduction of cells in the traumatized area.

Stenosis, restenosis, and cancerous growth or tumors may block other body passageways besides coronary arteries, including the esophagus, bile ducts, trachea, intestine, and the urethra, among others.

In an effort to prevent or minimize restenosis after medical procedure that opens a bodily lumens, various systems and methods have been proposed to locally deliver pharmacological agents such as rapamycin, an immunosuppressant known for its anti-proliferation properties, or paclitaxel, a chemotherapy agent and microtubular stabilizer that causes cells to stop dividing due to a mitotic block between metaphase and anaphase of cell division. Some of these inhibitory pharmacological agents have the potential to interfere or delay healing, weakening the structure or elasticity of the newly healed vessel wall and damaging surrounding endothelium and/or other medial smooth muscle cells. Dead and dying cells release mitogenic agents that may stimulate additional smooth muscle cell proliferation and exacerbate stenosis.

The focused delivery of therapeutically effective drug levels is critical for optimizing the association of the inhibitory drug with its intracellular target, while minimizing intercellular redistribution of the drug to neighboring cells. Thus, various systems for delivering pharmaceutical agents to a targeted area of a vessel wall have been proposed. One drug-delivery system receiving much attention in recent years involves drug-eluting coatings for stents, which allow drugs to release during extended periods of time such as several weeks or months. For example, a medical device coating may express one or more therapeutic agents to inhibit smooth muscle cell proliferation, as described in "Implants Possessing a Surface of Endothelial Cells Genetically-Modified to Inhibit Intimal Thickening," Williams et al., U.S. Patent No. 5,957,972 granted September 28, 1999. The coating includes a monolayer of endothelial cells that are genetically modified to express the therapeutic agents and most specifically, the protein interferon-gamma. Polymer hydrogels also have been used to coat medical devices such as stents, as described in "Medical Devices Comprising Hydrogel Polymers Having Improved Mechanical Properties," Zhong et al., U.S. Patent No. 6,368,356 granted April 9, 2002. In these coatings, hydrogels are used to give a smoother surface for stent insertion or removal from the body.

Another proposed local drug-delivery system infuses a therapeutic agent into a biodegradable polymer stent. The challenge to using a biodegradable stent, however, is that the loading in and releasing of drugs may change the structural integrity and mechanical properties of the stent.

A third example of localized drug delivery is to provide a polymer sleeve or sheath that encompasses a portion of the stent, the sheath or sleeve comprising for example, bioabsorbable drug. Unfortunately, with this approach only a limited number of drugs can be combined into solid-state polymers. In another example, a drug is disposed between two layers, preferably of polymers, which are located on either the inside or outside luminal walls of the stent, as described in "Stent Having Cover with Drug Delivery Capability," Yang, U.S. Patent No. 6,613,084 granted September 2, 2003. An anti-thrombogenic, lubricious coating for metallic medical devices has been developed to release sustained, therapeutic amounts of nitric oxide, as disclosed in "Nitric Oxide-Releasing Metallic Medical Devices," Fitzhugh et al., U.S. Patent No. 6,270,779 granted August 7, 2001.

While restenosis from hard-plaque obstructions can be a cause of myocardial infarction, known commonly as a heart attack, recent medical research suggests that the development and rupture of non-occlusive, soft atherosclerotic or vulnerable plaques in coronary arteries may play a greater role in heart attacks than restenosis caused from hard plaques. Research suggests that vulnerable plaques have a dense infiltrate of macrophages within a thin fibrous cap that overlies a pool of lipid. The rupture of vulnerable plaques, due to inflammatory processes and mechanical stress like increased blood pressure, results in exposure of blood to the lipid core and other plaque components. Vulnerable plaque erodes or ruptures, creating a raw tissue surface that forms scabs, and pieces of plaque that break off may accumulate in the coronary artery to create a thrombus of sufficient size to slow down or stop blood flow.

Vulnerable plaque is ingrained under the arterial wall and is difficult to detect with conventional means such as angiography or fluoroscopy. Thermography, which is capable of detecting a temperature difference between atherosclerotic plaque and healthy vessel walls, is one of the imaging methods being pursued for locating vulnerable plaque.

Unnecessary tissue damage continues to be an issue for many percutaneous procedures and endoluminal treatments of diseased vessels. Therefore, improved systems, methods and devices for treating diseased organ lumens and endoluminal vessels minimize or eliminate damage to surrounding tissue and prevent restenosis of treated areas. The desirable treatment of specific tissues provides mechanical support for the lumen and sustained local delivery of therapeutic compositions to help tissue to heal while avoiding excessive drug levels. More specifically, improved methods and devices for treating coronary artery disease minimize inflammation, restenosis, and the ingrowth of host tissue proliferation; control the dosage and delivery of therapeutic components to vascular tissue and smooth muscle cells over extended periods of time; successfully treat vulnerable plaque; and treat or prevent undesirable medical conditions within a vessel.

SUMMARY OF THE INVENTION

One aspect of the invention is a coated stent including a stent latticework and an alginate coating disposed on the stent latticework.

Another aspect of the invention is a method of treating a vessel in a mammalian body. The method includes the steps of providing a stent latticework and coating the stent latticework with an alginate solution to form a coated stent having an alginate coating disposed on the stent latticework. The coated stent is positioned within the vessel and deployed. A therapeutic agent is eluted from the alginate coating.

Another aspect of the invention is an alginate coating for an implantable medical device. The alginate coating includes an alginate matrix and one of a therapeutic component or a cellular component dispersed within the alginate matrix.

BRIEF DESCRIPTION OF THE DRAWINGS

The aforementioned, and other features and advantages of the invention will become further apparent from the following detailed description of the presently preferred embodiments, read in conjunction with the accompanying drawings. The detailed description and drawings are merely illustrative of the invention rather than limiting, the scope of the invention being defined by the appended claims and equivalents

thereof. Various embodiments of the present invention are illustrated by the accompanying figures, the figures not necessarily drawn to scale, wherein:

FIG. 1 illustrates a coated stent, in accordance with one embodiment of the current invention;

FIG. 2 illustrates a cross-sectional view of the coated stent of **FIG. 1**;

FIG. 3 illustrates a coated stent deployed in a vessel, in accordance with one embodiment of the current invention;

FIG. 4 is a schematic diagram of a method for coating an implantable medical device, in accordance with one embodiment of the current invention; and

FIG. 5 is a flow diagram of a method of treating a vessel in a mammalian body, in accordance with one embodiment of the current invention.

DETAILED DESCRIPTION OF THE INVENTION

FIG. 1 illustrates a coated stent, in accordance with one embodiment of the present invention. **FIG. 2** illustrates a cross-sectional view of the coated stent of **FIG. 1**, with like-numbered elements referring to similar or identical elements in each illustration. **FIG. 1** and **FIG. 2** taken together, coated stent **10** includes a stent latticework **20** with an alginate coating **30** disposed on stent latticework **20**. Alginate coating **30** provides a protective coating for stent latticework **20** to minimize, for example, emission of metal ions. Alginate coating **30** provides a mechanism for controlled, time-release characteristics of therapeutic agents **40** from any therapeutic components **34** and cellular components **36** within an alginate matrix **32** of alginate coating **30**. In one embodiment, the invention provides localized delivery of one or more therapeutic agents **40** from therapeutic components **34** dispersed within alginate coating **30** when coated stent **10** is deployed within a vessel of a mammalian recipient. In another embodiment, the invention provides long-term delivery of one or more therapeutic agents **40** via a matrix suitable for maintaining encapsulated cells and aggregates of viable cells from transplanted or implanted cells that produce such therapeutic agents.

Stent latticework **20** or other implantable medical devices are covered with a relatively thin coating of alginate matrix **32** including selected therapeutic components **34** and cellular components **36** that produce therapeutic agents **40** for elution from alginate coating **30**. In the case of cellular components **36**, alginate matrix **32** serves as an immune barrier so that the immune system of the recipient does not recognize cellular component **34** contained within alginate matrix **32** and destroy the cell and terminate the production of therapeutic agents **40**, while alginate matrix **32** allows for the metabolic transfer of nutrients, wastes, and therapeutic proteins and agents to pass through alginate matrix **32** into the surrounding vessel. Therapeutic agents **40** are delivered in close proximity to the treatment site. With imbibed cellular and therapeutic components, long-term expression of the therapeutic agents **40** from alginate coating **30** may be provided.

One example of a cellular component is endothelial cells that produce nitric oxide, a regulating molecule for smooth muscle cell quiescence and maintenance of vascular smooth muscle cells in the non-proliferative stage. A patient's own endothelial cells from, for example, microvascular adipose tissue may be harvested and mixed with an alginate solution, and applied to the surfaces of stent latticework **20**. Upon implantation, the cells remain viable and locally produce nitric oxide to regulate and maintain the quiescent nature of smooth muscle cells, which can be a contributor to the production and recruitment of fibroblasts from the media and adventitia of arteries. With the continued long-term production of nitric oxide from the translocated endothelial cells, vascular patency may be maintained for a period substantially longer than the period for potential stenotic reoccurrence following stent placement.

Stent latticework **20** of coated stent **10** may comprise, for example, a metallic body or a polymeric body. Metallic bodies include a metal such as stainless steel, nitinol, platinum, or a suitable biocompatible metal alloy. Polymeric bodies include, for example, a bio-absorbable polymer such as poly-L-lactide or other bio-erodable polymers suitable for implantation within the body.

Stent latticework **20** of coated stent **10** may be balloon-expandable or self-expandable, stent configurations that are well known in the art. Balloon-expandable stents are often crimped onto an inflatable polyurethane balloon that is coupled near a

distal end of a catheter body. Inflation lumens within the catheter body allow an inflation fluid to be transported into and out from an interior region of the inflatable balloon. When coated stent **10** is appropriately positioned within the vessel, the stent is expanded by inflating the balloon, thereby enlarging stent latticework **20** and deforming the latticework against the endoluminal wall of the vessel to provide mechanical support and allow for elution of one or more therapeutic agents **40** from alginate coating **30**.

Alternatively, a self-expandable stent latticework **20** expands and presses against endoluminal walls of the vessel when a deployment sheath is pulled away from the stent latticework so that the compressed stent latticework freely expands towards its original expanded shape.

Alginate coating **30** includes alginate matrix **32**, and may include one or more therapeutic components **34** and cellular components **36**. Alginate coating **30** controls the elution of one or more therapeutic agents **40** from either therapeutic components **34** or cellular components **36** from alginate coating **30**. Alginate coating **30** comprises alginate matrix **32** with, for example, crosslinked chains of mannuronate alginate monomers **62** and guluronate alginate monomers **64**. A predetermined ratio of mannuronate alginate monomers **62** and guluronate alginate monomers **64** may be selected to provide the desired elution rates for therapeutic agents **40**. Alginate, which may be extracted from brown seaweeds such as Phaeophyceae and Laminaria, is a linear copolymer with homopolymeric blocks of mannuronate alginate monomers and guluronate alginate monomers, respectively, covalently linked together in different sequences or blocks.

The alginate monomers can appear in homopolymeric blocks of consecutive guluronate alginate monomers **64**, consecutive mannuronate alginate monomers **62**, alternating mannuronate alginate monomers **62** and guluronate alginate monomers **64**, or randomly organized blocks. The relative amount of each block type varies with the origin of the alginate. Alternating blocks of mannuronate alginate monomers **62** and guluronate alginate monomers **64** form the most flexible chains and are more soluble at lower pH than the other block configurations. Blocks of guluronate alginate monomers **64** form stiffer chain elements, and two guluronate alginate monomeric blocks of more than six monomers each form stable crosslinked junctions with divalent cations such as

Ca^{2+}, Ba^{2+}, Sr^{2+}, and Mg^{2+} leading to a three-dimensional gel network or alginate matrix.

At low pH, protonized alginates form acidic gels. The homopolymeric blocks form the majority of the junctions, and the relative content of guluronate alginate monomers **64** determines the stability of the gel.

Alginate gels can develop and set at temperatures close to room temperature. This property is particularly useful in applications involving fragile materials like cells or tissue with low tolerance for higher temperatures.

The alginate polymers serve as thermally stable cold-setting gelling agents in the presence of divalent cations such as calcium ions from calcium sources. Gelling depends on the ion binding, with the divalent cation addition being important for the production of homogeneous gels, for example, by ionic diffusion or controlled acidification of calcium carbonate. High guluronate alginate monomer content may produce strong, brittle gels with good heat stability, whereas high mannuronate alginate monomer content produces weaker, more elastic gels. At low or very high divalent calcium concentrations, high mannuronate alginates produce stronger gels. When the average chain lengths are not particularly short, the gelling properties correlate with the average guluronate alginate monomer block length having an optimum block size of about twelve monomers, and do not necessarily correlate with the ratio of mannuronate alginate monomers **62** to guluronate alginate monomers **64**, which may be due primarily to alternating mannuronate-guluronate chains. Recombinant epimerases with different specificities may be used to tailor mechanical and transport characteristics of the alginate.

The solubility and water-holding capacity of the alginate depends at least on pH, molecular weight, ionic strength, and the nature of the ions present. Alginate tends to precipitate below a pH of about 3.5. Alginate with lower molecular weight calcium alginate chains of less than 500 monomers shows increasing water binding with increasing size. Lower ionic strength of alginate increases the extended nature of the calcium alginate chains. An alginate gel develops rapidly in the presence of divalent cations like Ca^{2+}, Ba^{2+}, Sr^{2+}, or Mg^{2+} and acid gels may also develop at low pH. Gelling of the alginate premix occurs when divalent cations take part in the interchain

ionic binding between guluronate alginate monomer blocks in the polymer chain, giving rise to a three-dimensional network. Alginates with a high content of guluronate alginate monomer blocks tend to induce stronger gels. Gels made of mannuronate-rich alginate are often softer and more fragile, with a lower porosity, due in part to the lower binding strength between the polymer chains and to the higher flexibilities of the molecules.

The gelling process is highly dependent on diffusion of gelling ions into the polymer network. Methods that may be used for the preparation of alginate gels include dialysis/diffusion and internal gelling.

In the dialysis/diffusion or diffusion-setting method, gelling ions are allowed to diffuse into the alginate solution. This method is commonly used for immobilization of living cells in the alginate gel. An alginate solution can also be solidified by internal gelation, internal setting, or in situ gelling. A calcium salt with limited solubility or complexed divalent calcium ions may be mixed into an alginate solution, resulting in the release of calcium ions, usually by the generation of acidic pH with a slowly acting acid such as D-glucono-α-lactone. The resultant alginate is a homogenous alginate macrogel. Diffusion setting and internal setting of the alginate matrix have different gelling kinetics and result in differences in their gel networks.

In one embodiment, therapeutic components **34** may be dispersed within alginate coating **30**. Therapeutic component **34** within coated stent **10** include, for example, an anti-coagulant, an anti-platelet drug, an anti-thrombotic drug, an anti-proliferant, an inhibitory agent, an anti-stenotic substance, heparin, a heparin peptide, an anti-cancer drug, an anti-inflammatant, nitroglycerin, L-arginine, an amino acid, a nutraceutical, an enzyme, a nitric oxide synthase, a diazeniumdiolate, a nitric oxide donor, rapamycin, a rapamycin analog, paclitaxel, a paclitaxel analog, a coumadin therapy, a lipase, or a combination thereof. Therapeutic agents **40** released from alginate coating **30** having therapeutic components **34** include, for example, the components themselves or portions thereof.

In another embodiment, coated stent **10** may include one or more cellular components **36** dispersed within alginate coating **30**. Cellular component **36** controllably releases therapeutic agent **40** when coated stent **10** is deployed within a vessel of a

mammalian body. Cellular component **36** within coated stent **10** may include, for example, endothelial cells, manipulated cells of designer deoxyribonucleic acid, host-derived cells from a host source, donor-derived cells from a donor source, pharmacologically viable cells, freeze-dried cells, or a combination thereof. Therapeutic agents **40** released from alginate coating **30** having cellular components **36** include, for example, a residue, a byproduct, or natural excretion from the cells.

Therapeutic agents **40** released from coated stent **10** with therapeutic components **34** or cellular components **36** include, for example, nitric oxide. Other examples of therapeutic agents **40** include vascular endothelial growth factor, a biological anti-inflammatory agent, vitamin C, acetylsalicylic acid, a lipid lowering compound, a high-density lipoprotein cholesterol, a streptokinase, a kinase, a thrombolytic agent, an anti-thrombotic agent, a blood-thinning agent, a coumadin material, an anti-cancer agent, a therapeutic component, a cellular component, or a combination thereof.

Living cells or other biomaterials and therapeutic compounds may be immobilized in alginate matrix **32** such as an alginate gel. Cells immobilized in alginate gels maintain good viability during long-term culture, due in part to the mild environment of the gel network. Alginate gel provides a physically protective barrier for immobilized cells and tissue, and inhibits immunological reactions of the host.

Alginate matrix **32** provides a location that is viable and productive for cellular components **36**. This viable and productive location is possible because alginate matrix **32** allows diffusion of nutrients to the cell, diffusion of respiratory byproducts to the surrounding area, and diffusion of selected therapeutic components **34** in an unaltered condition from alginate matrix **32**. In some cases, alginate matrix **32** serves as an immune barrier while providing for diffusive transport for therapeutic and cellular materials. The immune barrier properties of alginate matrix **32** are particularly useful for non-host derived cell sources, or manipulated cells of designer deoxyribonucleic acid (DNA).

In one example, long-term administration of at least one therapeutic agent **40** such as nitric oxide is provided to a mammalian vessel that is procedurally traumatized, for example, by an angioplasty procedure. Endothelial-derived nitric oxide is a naturally

occurring regulation compound. The endothelial cell lining of vessels produces the nitric oxide molecule. Endogenously produced nitric oxide is produced by the endothelial cell in such a manner that the uptake of the molecule regulates the proliferation of the vascular smooth muscle cells and maintains the cellular quiescence of smooth muscle cells within the vascular architecture. Nitric oxide is critical to numerous biological processes, including vasodilation, neurotransmission, and macrophage-mediated microorganism and tumor killing. Nitric oxide may be administrated in a chemically synthesized form as a nitric oxide donor, such as nitroglycerin dispersed within alginate matrix **32**.

Disruption of the endothelial lining in the vessel may result in the reduction of nitric oxide production, leading to the loss of regulation of the smooth muscle cells. This disruption can occur during stent placement, angioplasty, or from disease accumulation. Stent placement and angioplasty procedures that open an occluded vessel exert significant pressure on the luminal surface and may damage the endothelial cells.

Since it is such a small molecule, nitric oxide is able to diffuse rapidly across cell membranes and, depending on the conditions, is able to diffuse distances of more than several hundred microns, as is demonstrated by its regulation of smooth muscle cells, vascular dilation, tissue compliance and physiological tone of the vessel. Nitric oxide may be produced within alginate matrix **32** and delivered directly to the vessel. For example, L-arginine, a naturally occurring amino acid, and other nutraceuticals may be converted to nitric oxide within alginate matrix **32** by a group of enzymes such as nitric oxide synthases. These enzymes convert L-arginine into citrulline, producing nitric oxide in the process. In another example, nitric oxide is liberated from diazeniumdiolates, compounds that release nitric oxide into the blood stream and vascular walls.

FIG. 2 illustrates a cross-sectional view of the coated stent of **FIG. 1**, taken through line A-A'. Coated stent **10** includes a stent latticework **20** and an alginate coating **30** disposed on stent latticework **20**. Since alginate coating **30** is thin relative to the intracellular spacing between struts of stent latticework **20**, alginate coating **30** individually envelops the struts and other members of stent latticework **20**.

Alginate coating **30** includes an alginate matrix **32** with one or more therapeutic components **34** or cellular components **36** dispersed within alginate coating **30**. For example, therapeutic components **34** and cellular components **36** can be either uniformly dispersed throughout alginate coating **30**, or have a non-uniform profile with a higher concentration of therapeutic components **34** or cellular components **36** nearer the struts of stent latticework **20** or closer to an outer surface of alginate coating **30**. In another example, therapeutic components **34** and cellular components agglomerate or collect in regions of alginate coating **30**.

Alginate coating **30** may have crosslinked chains of mannuronate alginate monomers **62** and guluronate alginate monomers **64** in a predetermined ratio to provide the desired mechanical strength and flexibility while controlling the elution rates for therapeutic agents **40**.

FIG. 3 illustrates a coated stent deployed in a vessel, in accordance with one embodiment of the present invention. In either a balloon-expandable or self-expanding configuration, a coated stent **10** with a stent latticework **20** and an alginate coating **30** is deployed in a vessel **50** of a body **52**. Vessel **50** has a partial occlusion or stenosed region **54** that blocks the flow of fluid through vessel **50**. With coated stent **10** deployed in stenosed region **54**, endoluminal walls **56** are locally expanded outward to reduce the constriction and allow for increased fluid flow through the vessel.

Alginate coating **30** includes an alginate matrix **32** and one or more therapeutic components **34** or cellular components **36**. Therapeutic components **34** and cellular components **36** elute one or more therapeutic agents **40** when coated stent **10** is deployed in vessel **50** of body **52**. Therapeutic agents **40** elute from alginate coating **30** through endoluminal wall **56** of vessel **50** and into various tissues of stenosed region **54** and vessel **50** near the deployed stent.

FIG. 4 is a schematic diagram of a method for coating an implantable medical device, in accordance with one embodiment of the present invention. An alginate coating **30** for an implantable medical device **12** includes an alginate matrix **32** and a therapeutic component **34** dispersed within alginate matrix **32**. Alternatively, alginate coating **30** for implantable medical device **12** includes alginate matrix **32** and cellular component **36**

dispersed within alginate matrix **32**. Alginate coating **30** may contain one or more therapeutic components **34** and cellular components **36** dispersed within alginate matrix **32**.

Alginate coating **30** is formed or otherwise deposited on exposed portions of implantable medical device **12** to provide, for example, mechanical protection and controlled, time-released delivery of therapeutic agents **40** from either therapeutic components **34** or cellular components **36** dispersed within alginate coating **30**. In one embodiment, alginate coating **30** with alginate matrix **32** encapsulates and maintains the viability of cellular components **36** and allows the expression of therapeutic agents **40** from the cells to pass through alginate matrix **32** and elute into surrounding target tissues such as arterial tissues.

A ratio of mannuronate alginate monomers **62** and guluronate alginate monomers **64** may be selected to provide a predetermined elution characteristic of the alginate coating.

An alginate premix of mannuronate alginate monomers **62** and guluronate alginate monomers **64**, an alginate solvent **66** such as alcohol or water, and one or more therapeutic components **34** and cellular components **36** are combined to form an alginate solution with the determined ratio of mannuronate alginate monomers **62** and guluronate alginate monomers **64**. An alginate linking agent **68** is added to alginate solution **60**. Implantable medical device **12** such as a stent latticework is coated with alginate solution **60**, where the alginate crosslinks, gels, and hardens to coat external surfaces of implantable medical device **12**.

Alginate coating **30** may be coated onto implantable medical device **12** such as a stent, a valve, a pacemaker lead, a pacemaker, a pacing device, a venous filter, an abdominal aortic abdominal aneurysm device, or a vascular graft.

FIG. 5 is a flow diagram of a method for treating a vessel in a mammalian body, in accordance with one embodiment of the present invention. Treatable vessels include, for example, a coronary vessel, a cardiovascular vessel, a carotid artery, a hepatic vein, a hepatic artery, an artery, a vein, a peripheral vessel, an esophagus, a bile duct, a trachea, an intestine, a urethra, or a colon. The method includes various steps to form a coated

stent or other implantable medical device and to treat or prevent a medical condition in the vessel. Fabrication of the coated stent may occur remotely to, or in some cases, within a clinical setting so that donor-provided cells may be harvested and combined with the coating material immediately prior to implantation of the device.

A stent latticework is provided, as seen at block **80**. The stent latticework may be balloon-expandable or self-expandable, and may have a body including a metal such as stainless steel, nitinol, platinum, or a biocompatible metal alloy. Alternatively, the stent latticework may have a polymeric body comprised of a polymer such as poly-L-lactide. The length, expanded diameter, and compressed diameter of the stent are selected in accordance with the vessel to be stented.

The desired therapeutic components and cellular components are selected, as seen at block **82**. Selectable therapeutic components include, for example, an anti-coagulant, an anti-platelet drug, an anti-thrombotic drug, an anti-proliferant, an inhibitory agent, an anti-stenotic substance, heparin, a heparin peptide, an anti-cancer drug, an anti-inflammatant, nitroglycerin, L-arginine, an amino acid, a nutraceutical, an enzyme, a nitric oxide synthase, a diazeniumdiolate, a nitric oxide donor, rapamycin, a rapamycin analog, paclitaxel, a paclitaxel analog, a coumadin therapy, a lipase, or a combination thereof. Selectable cellular components include, for example, endothelial cells, designer-DNA manipulated cells, host-derived cells from a host source, donor-derived cells from a donor source, pharmacologically viable cells, freeze-dried cells, or combinations thereof.

Based on the desired elution characteristics of the therapeutic and cellular components, the ratio of mannuronate alginate monomers and guluronate alginate monomers may be determined. For example, the block length of mannuronate alginate monomers and the block length of guluronate alginate monomers are selected to achieve suitable strength and flexibility of the coated device, while providing controlled delivery of therapeutic and cellular components dispersed within the alginate matrix. The dose and constituency of added therapeutic and cellular components may be selected based on the desired treatment of the vessel.

In one example, an alginate premix is sterilized by its passage through a selection of submicron filters, by exposure to radiation in the form of ionizing gamma or electron

beams, or by other known methods of rendering a viscous solution sterile. The premix may be mixed in a solution prior to filtration and then dried, for example, by dialysis or spray drying.

In another example, the mannuronate alginate monomers, guluronate alginate monomers, and an alginate solvent such as alcohol or water are mixed to form the alginate solution with the determined ratio of mannuronate alginate monomers and guluronate alginate monomers. The concentration and viscosity of the alginate solution may be reduced with the addition of aqueous cellular or therapeutic components.

In an optional step, one or more viable cell components may be harvested from a host or donor mammalian body, as seen at block **84**. The harvested viable cellular component comprises, for example, endogenous endothelial cells. The harvested cells may be further cultured to increase their numbers or further filtered to obtain the desired quantity, quality and type of cell. In one example, the harvested viable cellular component is mixed into the alginate solution prior to coating the stent latticework. In another example, freeze-dried cells are mixed into the alginate solution with for, example, an aqueous-based alginate solvent. The freeze-dried cells are reconstituted when the coated stent is inserted and deployed in the body.

In another example, cells from either a host or donor source are preserved with trehalose and freeze-dried, rendering the cells functional yet in a dehydrated state. The cells are mixed into the alginate solution and coated onto the stent or implantable biomedical device. Use of cells in a preserved fashion allows for manufacturing of the coated device in advance of a medical procedure. The cells are preserved with the trehalose and protected by the immune barrier of the alginate matrix. One skilled in the art can identify alternative cell-producing components that can be substituted for endothelial cells and provide therapeutic products from the alginate matrix.

The selected therapeutic components and cellular components are mixed with the determined ratio of mannuronate alginate monomers and guluronate alginate monomers or the alginate premix to form the alginate solution prior to coating the stent latticework, as seen at block **86**. For example, endothelial cells are mixed into a formulation of

alginate with appropriate mannuronate and guluronate components into an alginate solution, and the stent is coated with the cellularized alginate solution.

In one example, an alginate linking agent is added to the alginate solution, as seen at block **88**. The added alginate linking agent comprises, for example, divalent calcium, divalent barium, divalent strontium, divalent magnesium, or a source of calcium such as a calcium salt. The alginate linking agent may be added to the alginate solution immediately prior to coating the stent latticework or other implantable medical device, due to rapid gelling and setting of the alginate matrix. The alginate matrix is crosslinked, for example, with a divalent-cation solution such as a calcium solution. In another example, the alginate linking agent is applied to the stent latticework prior to the application of the alginate solution, and as it is applied, the alginate solution coagulates onto the stent latticework. In another example, the alginate linking agent is applied to a stent latticework previously coated with the alginate solution, causing the alginate solution to gel and harden accordingly. In another example, alternating alginate layers with varying ratios of mannuronate and guluronate monomers are incorporated onto the stent latticework, with an optional capping coat of abrasion and tear-resistant alginate. An alginate linking agent in a solution may be applied, for example, by dipping the alginate-coated device in a bath of divalent cation solution or by spraying the divalent cation solution onto the coated stent to initiate crosslinking, gelling and hardening. An alginate coating with multiple layers may be formed from successive dips into the same or different alginate solutions. Crosslinking and polymerization of the alginate solution may be activated at room temperature, or with exposure to ultraviolet light, infrared light, or thermal energy.

The stent latticework is coated with an alginate solution to form a coated stent having an alginate coating disposed on the stent latticework, as seen at block **90**. The alginate coating may include one or more therapeutic components or cellular components. The stent latticework may be coated by, for example, spraying, dipping, and rolling the stent latticework with the alginate solution at temperatures below, for example, 37 degrees centigrade. The alginate solution includes a plurality of alginate monomers and an alginate solvent, and may include one or more therapeutic components

or cellular components. The coated stent is dried and loaded onto a suitable catheter delivery system. The resulting device can be sterilized with conventional means that do not alter or damage the therapeutic or cellular components or the alginate matrix.

When used in a medical procedure, the coated stent is positioned within a vessel and deployed, as seen at block **92**. Positioning of the coated stent is accomplished, for example, by coupling the coated stent onto a delivery catheter, and advancing the coated stent to a treatment area by using a guidewire, as is known in the art. The coated stent is deployed, for example, by inflating and expanding an inflation balloon coupled to near the distal end of the catheter, or by retracting a sheath from a self-expanding stent latticework.

Once deployed, one or more therapeutic agents may be eluted from the alginate coating, as seen at block **94**. The alginate coating controls the elution of the therapeutic agent when the coated stent is deployed. In one example, the eluted therapeutic agent comprises nitric oxide from entrained endothelial cells to regulate the proliferation of smooth muscle cells in the vessel near the deployed stent. In another example, the cellular component in the alginate solution is reconstituted when the coated stent is deployed, and therapeutic agent is produced and delivered to the vessel.

While the embodiments of the invention disclosed herein are presently considered to be preferred, various changes and modifications can be made without departing from the spirit and scope of the invention. The scope of the invention is indicated in the appended claims, and all changes that come within the meaning and range of equivalents are intended to be embraced therein.

CLAIMS

What is claimed is:

1. A coated stent, comprising:

a stent latticework; and

an alginate coating disposed on the stent latticework.

2. The coated stent of claim 1, wherein the stent latticework comprises one of a metallic body or a polymeric body.

3. The coated stent of claim 2, wherein the metallic body comprises a metal selected from the group consisting of stainless steel, nitinol, platinum, and a biocompatible metal alloy.

4. The coated stent of claim 2, wherein the polymeric body comprises poly-L-lactide.

5. The coated stent of claim 1, wherein the stent latticework is balloon-expandable or self-expandable.

6. The coated stent of claim 1, wherein the alginate coating comprises an alginate matrix having a predetermined ratio of mannuronate alginate monomers and guluronate alginate monomers.

7. The coated stent of claim 1 further comprising:

a therapeutic component dispersed within the alginate coating, wherein the alginate coating controls the elution of a therapeutic agent from the alginate coating.

8. The coated stent of claim 7, wherein the therapeutic component is selected from the group consisting of an anti-coagulant, an anti-platelet drug, an anti-thrombotic drug, an anti-proliferant, an inhibitory agent, an anti-stenotic substance, heparin, a heparin peptide, an anti-cancer drug, an anti-inflammatant, nitroglycerin, L-arginine, an amino acid, a nutraceutical, an enzyme, a nitric oxide synthase, a diazeniumdiolate, a nitric oxide donor, rapamycin, a rapamycin analog, paclitaxel, a paclitaxel analog, a coumadin therapy, a lipase, and a combination thereof.

9. The coated stent of claim 1 further comprising:

a cellular component dispersed within the alginate coating, wherein the cellular component controllably releases a therapeutic agent when the coated stent is deployed within a vessel of a mammalian body.

10. The coated stent of claim 9, wherein the cellular component is selected from the group consisting of endothelial cells, manipulated cells of designer deoxyribonucleic acid, host-derived cells from a host source, donor-derived cells from a donor source, pharmacologically viable cells, freeze-dried cells, and a combination thereof.

11. The coated stent of claim 9, wherein the released therapeutic agent comprises nitric oxide.

12. The coated stent of claim 9, wherein the released therapeutic agent comprises vascular endothelial growth factor, a biological anti-inflammatory agent, vitamin C, acetylsalicylic acid, a lipid-lowering compound, a high-density lipoprotein cholesterol, a streptokinase, a kinase, a thrombolytic agent, an anti-thrombotic agent, a blood-thinning agent, a coumadin material, an anti-cancer agent, a therapeutic component, a cellular component, and a combination thereof.

13. A method of treating a vessel in a mammalian body, the method comprising:

providing a stent latticework;

coating the stent latticework with an alginate solution to form a coated stent having an alginate coating disposed on the stent latticework;

positioning the coated stent within the vessel;

deploying the coated stent; and

eluting a therapeutic agent from the alginate coating.

14. The method of claim 13, wherein the vessel of the mammalian body is selected from the group consisting of a coronary vessel, a cardiovascular vessel, a carotid artery, a hepatic vein, a hepatic artery, an artery, a vein, a peripheral vessel, an esophagus, a bile duct, a trachea, an intestine, a urethra, and a colon.

15. The method of claim 13, wherein coating the stent latticework comprises one of spraying, dipping, and rolling the stent latticework with the alginate solution, the alginate solution including a plurality of alginate monomers, an alginate solvent, and one of a therapeutic component or a cellular component.

16. The method of claim 13, wherein the alginate coating controls the elution of the therapeutic agent when the coated stent is deployed.

17. The method of claim 13, wherein the alginate coating includes one of a therapeutic component or a cellular component.

18. The method of claim 13, wherein the eluted therapeutic agent is selected from the group consisting of vascular endothelial growth factor, a biological anti-inflammatory agent, vitamin C, acetylsalicylic acid, a lipid lowering compound, a high-density lipoprotein cholesterol, a streptokinase, a kinase, a thrombolytic agent, an anti-

thrombotic agent, a blood-thinning agent, a coumadin material, an anti-cancer agent, a therapeutic component, a cellular component, and a combination thereof.

19. The method of claim 13, wherein the eluted therapeutic agent comprises nitric oxide to regulate the proliferation of smooth muscle cells in the vessel near the deployed stent.

20. The method of claim 13 further comprising:

determining a ratio of mannuronate alginate monomers and guluronate alginate monomers to provide a predetermined elution characteristic of the alginate coating;

mixing mannuronate alginate monomers, guluronate alginate monomers, an alginate solvent, and one of a therapeutic component or a cellular component to form an alginate solution with the determined ratio of mannuronate alginate monomers and guluronate alginate monomers;

adding an alginate linking agent to the alginate solution; and

coating the stent latticework with the alginate solution.

21. The method of claim 20, wherein the added alginate linking agent comprises one of divalent calcium, divalent barium, divalent strontium, or divalent magnesium.

22. The method of claim 13 further comprising:

selecting one of a therapeutic component or a cellular component; and

mixing the selected therapeutic component or the selected cellular component into the alginate solution prior to coating the stent latticework.

23. The method of claim 13 further comprising:

harvesting a viable cellular component from the mammalian body; and

mixing the harvested viable cellular component into the alginate solution prior to coating the stent latticework.

24. The method of claim 23, wherein the harvested viable cellular component comprises endogenous endothelial cells.

25. The method of claim 13 further comprising:

reconstituting a cellular component in the alginate solution when the coated stent is deployed.

26. An alginate coating for an implantable medical device, the alginate coating comprising:

an alginate matrix; and

one of a therapeutic component or a cellular component dispersed within the alginate matrix.

27. The alginate coating of claim 26, wherein the implantable medical device is selected from the group consisting of a stent, a valve, a pacemaker lead, a pacemaker, a pacing device, a venous filter, an abdominal aortic abdominal aneurysm device, and a vascular graft.

ABSTRACT OF THE DISCLOSURE

The invention provides a coated stent including a stent latticework and an alginate coating disposed on the stent latticework. A method of treating a vessel in a mammalian body and an alginate coating for an implantable medical device are also disclosed.

FIG. 1

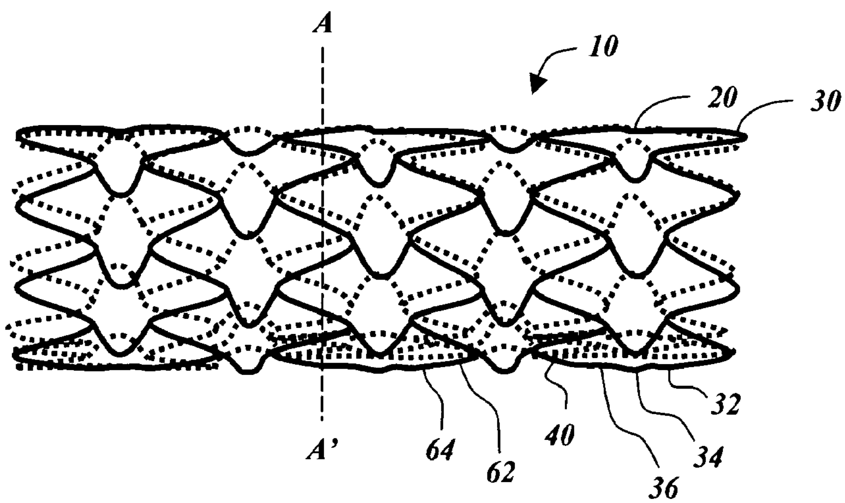


FIG. 2

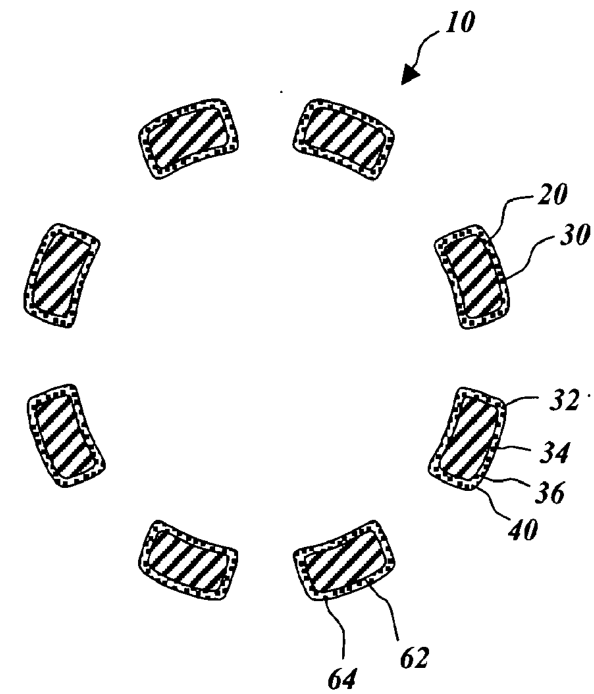


FIG. 3

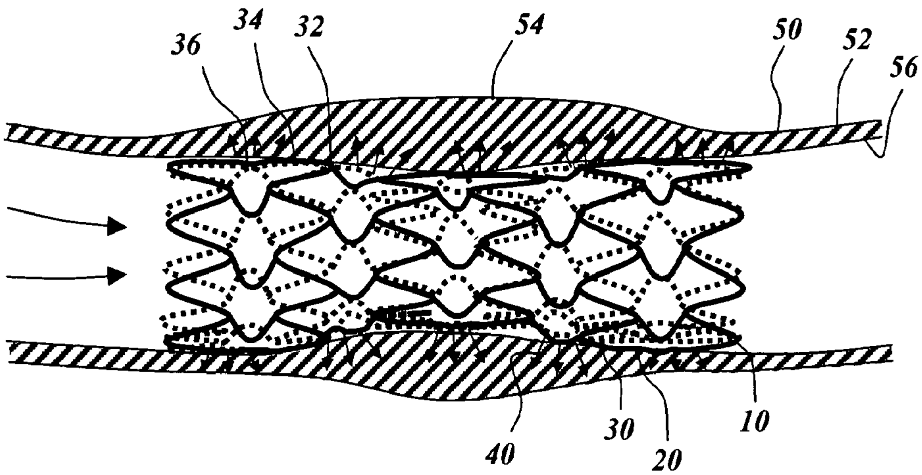


FIG. 4

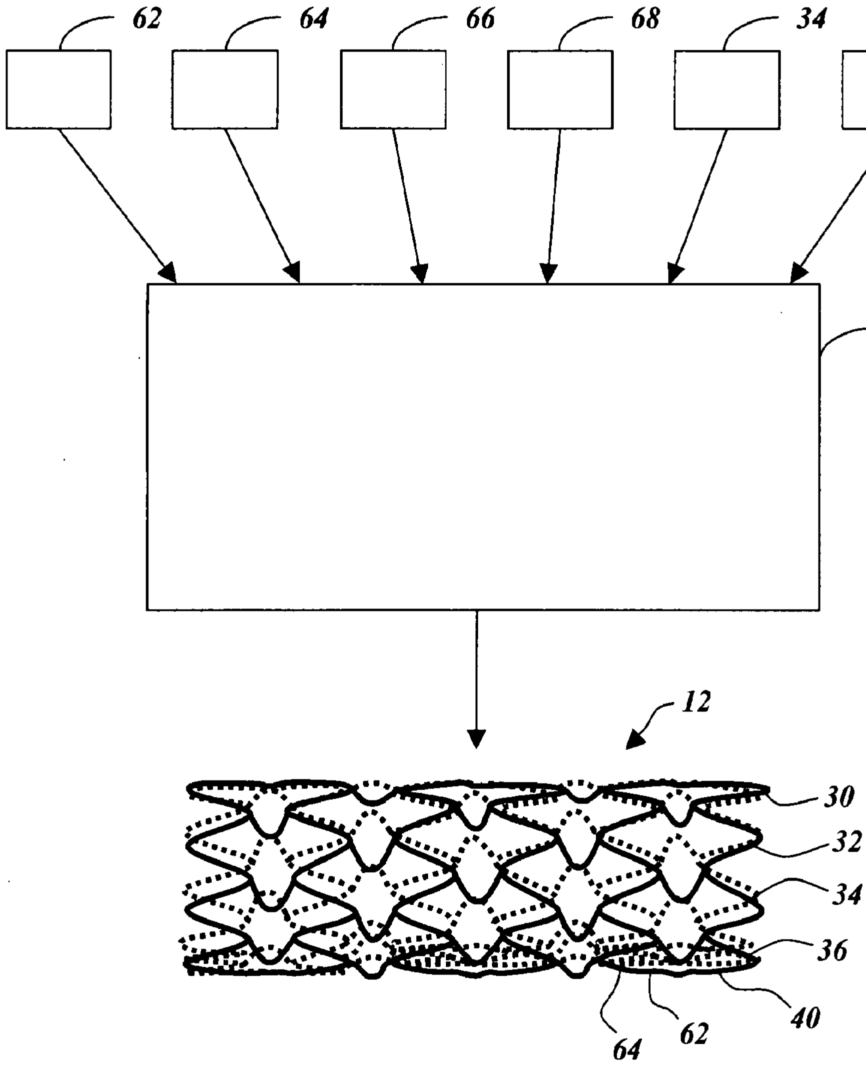
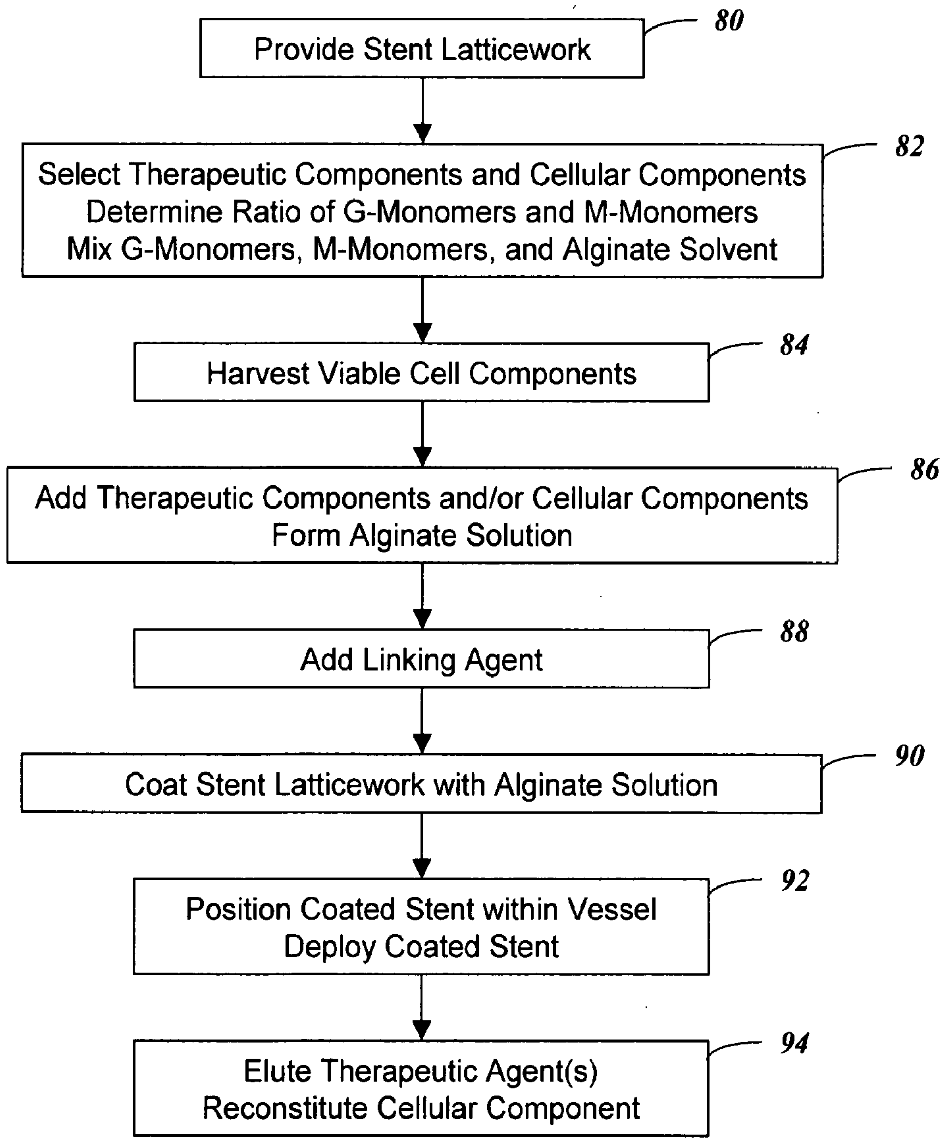


FIG. 5


80
Provide Stent Latticework
82
Select Therapeutic Components and Cellular Components
Determine Ratio of G-Monomers and M-Monomers
Mix G-Monomers, M-Monomers, and Alginate Solvent
84
Harvest Viable Cell Components
86
Add Therapeutic Components and/or Cellular Components
Form Alginate Solution
88
Add Linking Agent
90
Coat Stent Latticework with Alginate Solution
92
Position Coated Stent within Vessel
Deploy Coated Stent
94
Elute Therapeutic Agent(s)
Reconstitute Cellular Component